



# Killer cell Immunoglobulin-like Receptors (KIRs) and hematopoietic stem cell transplantation outcomes. A review of the literature



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## ABSTRACT

Natural killer (NK) cells are a type of cytotoxic lymphocytes that have an important role in innate immunity. These cells are equipped with a number of surface receptors, inhibitory, activating, or both, that control their activity. A major group of these regulatory receptors is called the Killer-cell Immunoglobulin-like Receptors (KIRs) which have been studied in numerous diseases. One of the most important aspects of KIR genotyping is its association with bone marrow transplantation outcomes; however, studies have not been conclusive in this regard. This is the first review article in the literature that reports on the association of KIR genotype with outcome of hematopoietic peripheral blood bone marrow stem cell transplantation using a four dimensional level of analysis based on the variable cellular interaction modalities of the KIR receptors: the ligand-ligand model, the missing-ligand model, the receptor-ligand model, and the haplotype model.

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## 1. Introduction

Natural killer (NK) cells are a type of cytotoxic lymphocytes that have an important role in innate immunity; they act against both virally infected and tumor cells. NK cells are constitutionally cytotoxic due to

the presence of cytoplasmic granules (containing *granzymes* and *perforin*) that lead to cell lysis or apoptosis. Usually, immune cells such as T cells recognize peptides presented by the Major Histocompatibility Class (MHC) molecules on the surface of infected or abnormal cells. NK cells, however, are unique in that they do not require this peptide presentation as part of their immune surveillance. They can recognize a cell as “self” and spare it by the presence of self-markers, namely MHC I molecules, which are present on all nucleated cells in our body; and thus whenever a cell is missing self-MHC I molecules (‘missing-self hypothesis’), it is considered as an altered self and destroyed by

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NK cells (Hsu et al., 2002). This is of crucial importance since it implies that an abnormal cell missing self-MHC I, be it an infected cell, a neoplastic cell, or an auto-reactive cell, that cannot be detected by T cells, can otherwise be recognized and destroyed by NK cells. The latter also have the ability to interact with components of the adaptive immune system (T cells and dendritic cells) implying their involvement in variable diseases such as infectious, autoimmune diseases, and cancers.

There are a number of surface receptors, inhibitory, activating, or both, that control NK cell activity. A major group of these regulatory receptors is called the Killer-cell Immunoglobulin-like Receptors (KIRs). KIRs are present additionally on a subtype of T cells, the cytotoxic T cells (Khakoo and Carrington, 2006). Most KIRs are inhibitory (iKIRs), meaning that their recognition of certain MHC I molecules inhibits the cytotoxic response of NK cells. Fewer identified KIRs are activating (aKIRs), but their ligand specificities have not yet been well elucidated (Khakoo and Carrington, 2006). Activation occurs when the NK cell receives a signal from the aKIRs that recognize affected or tumor cells that lack the normal HLA structures on its surface membrane (Impola et al., 2014).

Though KIR has been studied in a wide variety of clinical entities, be it for a negative or positive association, this review article will be focusing on the role of KIRs and their ligands in allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for hematologic malignancies.

One may speculate that NK cell alloreactivity contributes to what is called the *Graft-versus-tumor effect* (GVT), since a mismatched ligand or a missing ligand for a particular iKIR, taken independently, would mean the absence of inhibitory signal for NK cell cytotoxicity. By that, the NK cell would destroy the tumor cell with the mismatched or missing ligand for its iKIR. Consequently, this would lead to lower relapse rate and increased survival after the transplant. However, one should bear in mind that the selection of a related or unrelated HSCT donor needs matching of MHC molecules, also called HLA (for Human Leukocyte Antigens), to minimize *Graft-versus-Host Disease* (GVHD). Furthermore, the picture is complicated by the substantial variation in gene content and expression, allelic polymorphism, and haplotypic diversity of KIR genes. The ultimate goal is to try and elucidate which KIR profiles maximize antitumor while minimizing anti-host effects.

This unique review article sheds light on the various genotypes and haplotypes profiles of KIR in what concerns hematopoietic stem cell transplantation (HSCT) outcomes from a perspective that covers the different theories of KIR receptors interactions.

### 1.1. KIR haplotypes

KIR molecules are encoded by the Leukocyte Receptor Complex (LRC) present on human chromosome 19 which is segregated independently from the HLA genes. LRC is polygenic and individual genes exhibit polymorphism where 17 KIR genes are officially recognized (Dorak, 2007).

Two broad families can be identified according to the number of extracellular domains (designated KIR2D and KIR3D for 2 and 3 extracellular domains respectively), and the length of cytoplasmic tails (*S* for short and *L* for long). Generally, KIRs with long cytoplasmic tails are inhibitory (KIR2DL and 3DL groups) while those with short cytoplasmic tails are activating (2DS and 3DS groups) (Hsu et al., 2002). KIR2DL4 is an exception in that despite having a long cytoplasmic tail, it has both inhibiting as well as activating functions and is also present on all haplotypes (Beksaç and Dalva, 2012).

Based on the gene content, there has been segregation of KIR haplotypes into two basic groups: haplotype A and B.

Haplotype A, which is the most common one, is usually inhibitory as it contains 6 inhibitory genes: KIR2DL1, KIR2DL3 (most characteristic), KIR3DL1, KIR3DL2, KIR3DL3 and KIR2DL4 and one activating gene: KIR2DS4. These genes are more frequently found in haplotype A than B but are not exclusive to it and also have a substantial allelic diversity (Dorak, 2007).

Haplotype B, on the other hand, has a very diverse gene content in addition to minor allelic diversity. It is mostly activating and has a variable number of activating KIRs (ranging from 2 to 7), and a similar number of inhibitory KIRs than haplotype A. Certain genes, however, occur exclusively on haplotype B such as: KIR2DS1, KIR2DS2-2DL2 (most characteristic), KIR2DS3, KIR2DS5, KIR2DL2, KIR2DL5 and KIR3DS1 (Dorak, 2007).

Regarding the ligands, KIRs generally interact with MHC class I molecules with the exception of KIR2DS4 that interacts with HLA-Cw4 as well as non-MHC ligands. The specificities for iKIRs have been clearly defined for certain receptors. For example, KIR2DL1 binds HLA-C2 group, KIR2DL2/3 binds HLA-C1 group, KIR3DL1 binds HLA-B-Bw4, KIR3DL2 binds HLA-A, and KIR2DL4 binds HLA-G. As for the aKIRs, the specificities have been harder to define. For instance, KIR2DS1, 2DS2, and 3DS have the same ligands as KIR2DL1, 2DL2/3 and 3DL1, respectively, but bind weakly to them. Other KIRs have no known ligands yet (Khakoo and Carrington, 2006). Moreover, NK alloreactivity has been grouped into four models: The *KIR-ligand incompatibility* or *ligand-ligand model*, the *receptor-ligand model*, the *haplotype model* (*receptor-receptor* or *KIR gene-gene model*), and the *missing ligand model* (Beksaç and Dalva, 2012). However, the *receptor-ligand model* was not addressed in this manuscript due to the minute amount of data in the literature; further research should be done in order to account for it in such a review article. Table 1 summarizes the different authors' studies under model type and outcome.

The balance of inhibitory and activating KIRs determines the susceptibility or the protection against certain diseases such as viral infections, auto-immune diseases, and neoplastic transformations.

KIRs have been shown to play a role in HIV infection where individuals having the KIR3DS1 gene and homozygous for the HLA-B-Bw4 gene had a slower decline in CD4 + T-cell count, a marker of disease progression in HIV infected patients (Khakoo and Carrington, 2006). A similar protective role of KIR3DS1 and HLA-B-Bw4 was found in HCV infection and there was an additional increased frequency of KIR2DL3 in combination with HLA-C1 in patients who cleared of HCV infection compared to those who remained chronically infected (Khakoo and Carrington, 2006). KIR was also associated with the autoimmune disease rheumatoid arthritis as there was an expansion of CD4 + CD28 – T cells expressing the aKIR, KIR2DS2, in the absence of the corresponding iKIR in the peripheral blood of patients with rheumatoid arthritis. Additionally, in diabetes mellitus, an association, albeit weak, was found between KIR2DS2 and HLA-C1 group (Khakoo and Carrington, 2006).

The activity of NK cells against malignant cells has been known for a long time; however, it was only in the late 90s that the impact of KIR ligands on allogeneic HSCT was studied (Beksaç and Dalva, 2012). After an allogeneic HSCT, an NK cell receptor repertoire became established according to the KIR genes of the donor cells. NK cells can then contribute to GVT effect, as first demonstrated in T cell depleted haploidentical HSCT where this was shown to depend on *KIR ligand mismatch*. The contribution of *KIR ligand mismatch* to NK cell alloreactivity in unrelated HSCT was confirmed in some subsequent studies, but not in others (Clausen et al., 2010). In the setting of HLA-identical HSCT, however, NK cell alloreactivity must be explained by a mechanism other than *KIR ligand mismatch*, most likely by the *missing ligand* model (Beksaç and Dalva, 2012). In the latter model, NK cells may become uninhibited in the early post-transplant period, thus lysing target recipient cells for which corresponding ligands are absent (Bao et al., 2010a, 2010b). A hypothesis was built afterwards suggesting that allogeneic HSCT selected for lack of recipient HLA ligands for donor iKIRs would allow the development of alloreactive donor NK cells that could kill host tumor (GVT), because of the triggering effect of aKIR. Without an impedance by the iKIRs, binding of the aKIRs to their ligands would result in NK cell stimulation. The presence of more aKIR genes in donors further confirmed this as it was associated with a lower TRM and a better survival. However, this NK reactivity may also have a negative effect on outcome by

**Table 1**  
Corresponding authors' studies listed under outcome and model type.

Outcome	Model type	Author
Positive	Ligand-ligand	Duan et al. (2007)
		Beelen et al. (2005)
		Wang et al. (2013)
		Giebel et al. (2003)
		Zhang et al. (2011)
	Haplotype	Cooley et al. (2009)
		Bao et al. (2010a, 2010b)
		Kröger et al. (2006)
		Symons et al. (2010)
		Kanga et al. (2012)
	Missing-ligand	Wu et al. (2010)
		Clausen et al. (2012)
		Hsu et al. (2006)
		Wang et al. (2013)
		Van der Meer et al. (2008)
Negative	Ligand-ligand	Ludajic et al. (2009)
		Kröger et al. (2006)
		Zhao et al. (2008)
		De Santis et al. (2005)
		Giebel et al. (2009)
	Haplotype	Morishima et al. (2007)
		Elmaagacli et al. (2005)
		Bao et al. (2010a, 2010b)
		Bao et al. (2010a, 2010b)
		Cooley et al. (2009)
	Missing-ligand	Duan et al. (2007)
		Cook et al. (2004)
		Zhao et al. (2007)
		Wu et al. (2010)
		Van der Meer et al. (2008)
Neutral	Ligand-ligand	Kim et al. (2007a, 2007b)
		Miller et al. (2007)
		Ludajic et al. (2009)
		Clausen et al. (2012)
		Schaffer et al. (2004)
	Haplotype	Farag et al. (2006)
		Weisdorf et al. (2012)
		Sivula et al. (2007)
		Wu et al. (2010)
		Wongwuttisaraj et al. (2012)
Missing-ligand	Björklund et al. (2010)	
	Hsu et al. (2005)	
		Clausen et al. (2010)

increasing GVHD in unrelated HSCT when the donor has more aKIR (Bao et al., 2010a, 2010b). It is also noteworthy to mention that since KIR molecules are expressed on NK cells as well as a subset of T cells, it is possible that the presence of NK-cell alloreactivity might be associated with the presence of the T-cell alloreaction, thus increasing GVHD risk whenever the HSCT is not T cell depleted (Zhao et al., 2007).

Despite many advances in the studies, the extent to which NK cells and KIRs contribute to GVT and have a positive outcome in a HSCT remains controversial. The outcome of HSCTs was assessed as: incidence of GVHD, TRM, DFS, LFS, or OS and relapse. We will review and assess first the KIRs that had a positive outcome and then the ones that had a negative or neutral outcome.

### 1.2. KIR in HSCT: positive outcomes

Certain KIR and KIR ligands were found to be correlated with a positive outcome in bone marrow transplantation.

We begin by assessing how the number of KIR ligands, genes, and receptors can affect the aforementioned outcomes. Zhao X. et al. studied the impact of KIR ligands. In their study, they took into consideration the following KIR receptors and their ligands: KIR2DL1 with HLA-C2 related alleles, KIR2DL2/3 with HLA-C1 related alleles, and KIR3DL1 with HLA-Bw4 allele in patients with acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), non-Hodgkin's lymphoma (NHL), myelodysplastic syndrome

(MDS), and multiple myeloma (MM) who underwent unmanipulated HLA-haploidentical blood and marrow transplantation (Zhao et al., 2007). They found that the cumulative incidence of 3 year disease-free survival (DFS), OS, and TRM was best predicted by the number of KIR ligands in recipients. Patients with fewer KIR ligands were associated with either more frequent KIR ligand mismatch (*KIR ligand–ligand model*), more frequent KIR gene mismatch (*KIR gene–gene model*), or more frequent absence of KIR ligands in recipients for donor inhibitory KIR (*receptor–ligand model*). This suggested that an increased number of KIR ligands might be associated with less frequent NK-cell alloreaction. Considering that the degree of HLA disparity between donors and recipients was similar among the groups, it is possible that patients with more KIR ligands are associated with a decreased frequency of T-cell alloreaction. NK alloreaction has been demonstrated to prevent T-cell priming, thus reducing the incidence of acute graft versus host disease (aGVHD), while preventing relapse in the setting of HLA-haploidentical transplantation (Zhao et al., 2007).

The number of KIR receptors additionally affects the incidence of GVHD as demonstrated by De Santis et al. In this study, patients with ALL, AML, CML, MDS, lymphoma (Hodgkin's and non-Hodgkin's), and MM received unrelated donor bone marrow transplants in which there was considerable mismatching of donor and recipient at the HLA-C locus (C1 and C2) (De Santis et al., 2005). It was found that a greater number of KIR receptors, both aKIR and iKIR, in the donor protected against GVHD (grades III–IV) and improved survival (De Santis et al., 2005).

We also review the effect of the number of KIR genes on the incidence of aGVHD. Kim SY et al. investigated the association of KIR genes with aGVHD leukemia patients and their unrelated donors for HSCT (Kim et al., 2007a, 2007b). Donors with > 12 KIR genes showed significantly decreased frequencies of severe aGVHD compared to donors with < 11 KIR genes. There was no difference in the distribution of KIR genotypes between severe and mild acute GVHD in patients and donors, respectively. These results suggest that the number of KIR genes in donors could influence the occurrence of aGVHD after unrelated HSCT (Kim et al., 2007a, 2007b).

Dwelling more on the KIR genes, we see that the presence of specific genes in the donor was particularly important regarding outcome. This is illustrated, for example, in a study conducted by Kim HJ et al., whereby they investigated the influence of KIR genes, based on the genotypes of iKIRs or aKIRs, in stem cell recipients with AML and their HLA-matched sibling donors on acute GVHD after HSCT. They found that the 2DS1 gene was associated with a better long-term survival, even if present only in the donor and not the recipient (Kim et al., 2007a, 2007b). Complementing to these results just mentioned, after determining the KIR and HLA genotypes of related HLA-identical HSCT for patients with AML, CML, and ALL, Verheyden et al. found that the presence of two aKIRs, 2DS1, and 2DS2, in the donor was significantly associated with a decreased leukemic relapse rate (Verheyden et al., 2005). Moreover, the probability of relapse at five years was significantly lower for patients who received a graft from a donor with either or both the 2DS1 (+) and 2DS2 (+) genotypes than for those who received a transplant from other donors. This study, therefore, suggests that a joint effect of these two selected activating KIRs in the donor might confer some protection against leukemic relapse (Verheyden et al., 2005). The data suggest that the presence of the 2DS1 gene by itself as well as concomitantly with the 2DS2 gene in the donor was associated with better long-term survival. In addition, Wongwuttisaraj N. et al. analysed the outcomes of related HLA-identical HSCT in patients with leukemia. It was found that the presence of donor activating KIR2DS5 was associated with decreased aGVHD (Wongwuttisaraj et al., 2012). Thus, these findings suggest an important role of donor aKIR in identical sibling HSCT.

Nevertheless, an important point to be mentioned is that a given number of ligands can have different impacts on outcome depending on the disease stage. This is highlighted by Miller et al. through a

study conducted on AML, CML, and MDS patients undergoing unrelated donor HSCT (Miller et al., 2007). All patients had either 1, 2, or 3 KIR ligands (recipient C1, C2, and Bw4 KIR ligands). At a first glance, analysis revealed no differences in relapse or survival based on KIR ligand content in all the patients, however, after stratifying the patients according to disease stage, significant differences emerged. For patients with early disease (AML in first complete response, CML in first chronic phase and <1 year from diagnosis, or MDS with refractory anemia), the absence of 1 or more KIR ligands was protective against relapse as there was a decrease in relapse at 3 years from 11% to 6%. This finding was independent of HLA matching and independent of T cell depletion (Miller et al., 2007).

Furthermore, outcome depends not only on the disease stage but also on the type of leukemia in patients receiving bone marrow transplantation. Morishima et al. conducted a study on patients with leukemia (AML, ALL, and CML) who underwent transplantation with T-cell-replete marrow from an unrelated donor (UR-BMT). The GVL effect depended on leukemia cell type (Morishima et al., 2007). HLA-C mismatch reduced the relapse rate in ALL and HLA-DPB1 mismatch reduced it in CML (Morishima et al., 2007).

As we mentioned before, NK cell alloreactivity has been grouped into four models: *ligand-ligand model*, *receptor-ligand model*, *haplotype model*, and the *missing ligand model* (Beksaç and Dalva, 2012). We will discuss the outcome on bone marrow stem cell transplantation according to these models (except for the *receptor-ligand model* due to the minute amount of literature on the topic).

#### 1.2.1. Ligand-ligand model

The impact of KIR and its ligands on haploidentical BMT was investigated by Duan LN et al. who found that the DFS was significantly higher for the cases of mismatched KIR ligands (HLA-Cw) group than the matched group (Duan et al., 2007). Beelen et al. conducted a study on patients with myeloid leukemias (AML, CML, and MDS) who received unmodified allogeneic HSCT (Beelen et al., 2005). The most remarkable finding was a significant heterogeneity in the five-year estimates of hematologic leukemic relapse after HLA-identical, HLA class I-disparate, and KIR ligand mismatched transplantations. Moreover, the relative relapse risk was influenced by HLA class I disparity alone, but was lowest after HLA class I-disparate and KIR ligand-mismatched transplantations. However, they did not detect a beneficial effect of KIR ligand mismatch on other major outcomes of allogeneic HSCT (TRM, overall, and event-free survival). Beelen et al. concluded that unmodified allogeneic HSCT from KIR ligand-mismatched donors provides a superior long-term anti-leukemic efficacy in patients with myeloid malignancies (Beelen et al., 2005). Additionally, still in the context of myeloid malignancies, Wang H. et al. analysed the impact of interaction between recipient HLA-Cw and donor KIR on outcome in patients who received related HLA-matched HSCT. A lower incidence of chronic GVHD and higher OS and DFS were observed in the KIR-mismatched group (Wang et al., 2013).

Another study, by Giebel et al., evaluated patients with myeloid malignancies namely patients with ALL, AML, and CML given haploidentical T-cell-depleted HSCTs (Giebel et al., 2003). Patients were uniformly given GVHD prophylaxis that consisted of cyclosporin, short-term methotrexate, and pre-transplantation antithymocyte globulin (ATG). Patients were divided into those with and those without KIR ligand mismatch with respect to their donors. Within the patients receiving transplants from a KIR-mismatched donor, the KIR mismatch involved the HLA-C locus and HLA-B locus. At four years and a half, patients with KIR ligand mismatch had higher probability of OS and DFS compared with those without KIR ligand mismatch. TRM was lower in the group with KIR ligand mismatch (6% vs. 40%). Relapse rates for patients receiving transplants from a donor with KIR ligand mismatch were lower (6% vs. 21%). All patients with myeloid malignancies receiving transplants from KIR ligand-disparate donors are alive and disease free. These data indicate that KIR-ligand mismatch,

involving HLA-C and HLA-B loci, is associated with better outcome after unrelated donor HSC transplantation when ATG is used as part of GVHD prophylaxis (Giebel et al., 2003).

Patients with leukemia were the targeted population in other KIR studies. In particular, Zhang X. et al. conducted a study on leukemia patients who received haplo-identical HSCT (Zhang et al., 2011). Groups were classified according to match versus mismatch between donor's iKIR and recipient's HLA-C1/C2 subgroup. Two-year OS rate in the matched group was significantly higher than that in the mismatched group. Lower incidence of relapse rate was seen in the matched group than in the mismatched group. In 30 cases of myeloid leukemia patients, there was a lower relapse rate in the matched group than in the mismatched groups. Furthermore, according to the 3 aKIR genes: KIR2DS1/KIR2DS2/KIR2DS3, lower incidence of grade III-IV aGVHD was seen in KIR2DS1 (+) group than in KIR2DS1 (-) group; and so was done in KIR2DS3 (+) group. The relapse rate was lower in KIR2DS2 (+) group. But the latter results were not statistically significant. Zhang X. et al. concluded that in this haploidentical HSCT setting, match between donor's inhibitory KIR and recipient's HLA-C can significantly reduce the incidence of relapse rate and improve OS. Although lower incidences of severe aGVHD are noted in the donors with KIR2DS1 (+) or KIR2DS3 (+), and lower relapse rate is noted in the donors with KIR2DS2 (+) but without statistical difference, no remarkable effects of activating KIRs on OS have been found in this relatively small clinical series (Zhang et al., 2011).

#### 1.2.2. Haplotype model

Cooley S. et al. hypothesized that donor KIR genotype (A/A: 2 A KIR haplotypes; B/x: at least 1 B haplotype) would affect outcomes (Cooley et al., 2009). They genotyped donors and recipients from HLA-matched and mismatched T-replete URD transplantations for AML. Three-year OS was found to be significantly higher after transplantation from a KIR B/x donor. There was additionally a 30% improvement in the relative risk of RFS with B/x donors compared with A/A donors. This analysis demonstrated that unrelated donors with KIR B haplotypes conferred significant survival benefit to patients undergoing T-replete HCT for AML (Cooley et al., 2009). This correlation between haplotype B and positive outcome was similarly asserted by Bao X.J. et al. in their study conducted on leukemia patients (with CML, AML, and ALL) transplanted with T-depleted HSCT from unrelated donors. 60 patients (out of 75) were HLA 10/10 matched and 15 had some mismatches at HLA-C (Bao et al., 2010a, 2010b). They found that transplants from KIR haplotype B/x group donors had significantly higher OS rates compared with those from KIR haplotype A/A donors (Bao et al., 2010a, 2010b). This highlights the need to perform KIR genotyping of prospective donors, in addition to HLA typing, in order to identify HLA-matched donors with KIR B haplotypes.

Nevertheless, the presence of Haplotype A was actually found in one study to be associated with a positive outcome namely improved DFS and reduced relapse rate particularly in patients with AML, MDS, and CML. This was a finding, by Kroger N. et al., among 142 patients with leukemia, who received standard myeloablative conditioning followed by in vivo TCD (ATG) unrelated SCT (Kröger et al., 2006). SCT from donors with Haplotype A or with a low number of aKIR genes resulted in lower relapse rate with better DFS. These outcomes were only seen in AML, MDS, and to a lesser extent in CML but not in ALL. Consequently, after in vivo TCD (ATG) unrelated SCT with donors carrying low number of aKIR genes (haplotype A), the risk of relapse is decreased, leading to a significantly improved disease-free survival in patients with AML, MDS, and CML (Kröger et al., 2006).

Assessing the impact of KIR haplotype in the recipient, concomitant with that of the donor, is also important. In particular, Symons H.J. et al. examined the effect of KIR and HLA genotype, in both the recipient and donor, on the outcome of patients with advanced hematologic malignancies (for whom standard allogeneic (HLA-matched, related, or unrelated) or autologous BMT was unavailable or inappropriate) who

received nonmyeloablative, HLA-haploidentical HSCT (Symons et al., 2010). Compared to recipients of bone marrow from donors with identical KIR gene content, recipients of iKIR gene-mismatched BM had an improved OS, event-free survival (EFS), and relapse rate. Patients homozygous for the KIR A haplotype, which encodes only 1 activating KIR, had an improved OS, and nonrelapse mortality if their donor expressed at least 1 KIR B haplotype that encodes several activating KIRs. Thus, nonmyeloablative conditioning and T cell-replete, HLA-haploidentical HSCTs involving iKIR gene mismatches between donor and recipient, or KIR haplotype A/A recipients of BM from KIR B/x donors were associated with lower relapse and NRM and improved OS and EFS. These findings suggest that selection of donors based upon inhibitory KIR gene or haplotype incompatibility may be warranted (Symons et al., 2010).

Additionally, Kanga U. et al. conducted a study on patients with acute myeloid leukemia (AML) and acute lymphoid leukemias, lymphomas, aplastic anemia, and myelodysplastic syndrome (Kanga et al., 2012). All recipients underwent HSCT using HLA-identical sibling donors. While 84.5% of donors carried a KIR haplotype B/x, 15.5% carried the A/A haplotype. The presence of both C1 and C2 seemed to be protective against both forms of GVHD as lack of C1 may lead to manifestations of acute GVHD and lack of C2 to manifestation of chronic GVHD. The role of two Bw4 alleles, threonine (T) or isoleucine (I) at position 80, was evaluated. In this study, 73% of recipients carried the 80(I) allele while 27% carried the 80(T) allele. The presence of Bw4-80(T) allele appeared to reduce the risk of GVHD, indicating its stronger inhibitory effect than its 80(I) counterpart (Kanga et al., 2012). Thus, KIR-ligand interactions do influence HSCT outcomes.

In aggregate, these results suggested that combining KIR and HLA genotyping could help in the selection of transplant donors and improve the outcome of transplantation. **NK cell alloreactivity for leukemic patients that are receiving a KIR ligand mismatch HSCT is an advancement for a graft-vs-leukemic response and reduced GVHD** (Khanuntong et al., 2016).

### 1.2.3. Missing ligand model

Wu GQ et al. investigated the influence of KIRs on outcome after unrelated transplantation for patients with myeloid (AML, CML, and MDS) and lymphoid (ALL) leukemias (Wu et al., 2010). They found that missing KIR ligands in recipients were significantly associated with a decreased leukemic relapse risk, mainly in myeloid disease. This beneficial effect was seen in AML/MDS and also in CML. In myeloid disease, missing KIR ligands also improved the five-year OS and DFS. This study indicated that, in unrelated HSCT for myeloid leukemia, missing KIR ligands in recipients offered a lower relapse risk and a long-term survival advantage (Wu et al., 2010).

We note that recipient homozygosity for HLA-B or -C KIR epitopes predicts lack of KIR ligand. Of particular importance are the HLA-C1/C2 and Bw4 KIR ligands mentioned. Further studies emphasized the impact of these ligands with varying outcomes.

Some studies revealed good outcome associated with HLA-C2 homozygosity and missing HLA-Bw4 ligand. In fact, Clausen J. et al. analysed the effects of missing HLA-C1/2 and Bw4 KIR ligands in patients with myeloid (AML, CML, MDS) and lymphoid (ALL, HL, NHL) leukemias and myelomas on the outcome in HSCT, comparing bone marrow transplant (BMT) to peripheral blood stem cell transplants (PBSCT) (Clausen et al., 2012). C2 homozygosity was not found to be unfavorable after BMT. C2 homozygous recipients had better progression-free survival (PFS) after BMT than after PBSCT, due to fewer relapses. Missing Bw4 favorably influenced PFS after BMT but not after PBSCT (Clausen et al., 2012).

Other studies showed that missing both HLA-C2 as well as HLA-Bw4 ligands was associated with a good outcome. Hsu et al. evaluated KIR ligand effect on risk of relapse in patients undergoing myeloablative T-replete HCT from HLA-matched or mismatched unrelated donors for the treatment of myeloid and lymphoid leukemias. In the case of HLA-mismatched unrelated donors, absence of HLA-C2 or HLA-Bw4 KIR ligands

in the recipient was associated with lower hazards of relapse. Therefore, recipient homozygosity for HLA-B or -C epitopes that define KIR ligands is likely to be a predictive factor for leukemia relapse after myeloablative HCT from HLA-mismatched unrelated donors (Hsu et al., 2006).

Moreover, homozygosity in either HLA-C1 or C2 was shown to be associated with better outcome than C1/C2 heterozygosity. Wang H. et al. analysed the impact of interaction between recipient HLA-Cw and donor KIR on outcome in patients who received related HLA-matched HSCT for myeloid malignancies (Wang et al., 2013). The incidence of chronic GVHD was found to be significantly lower in C1 or C2 homozygotes than in C1/C2 heterozygotes. Higher OS and DFS rates were observed in C1 or C2 homozygotes than in C1/C2 heterozygotes (Wang et al., 2013). A similar correlation was found in a study conducted by Clausen J. et al. on patients with leukemias, lymphomas, and myelomas who underwent HLA-identical sibling transplantations as they found that C1/2 heterozygous patients had a favourable risk ratio for relapse, relapse-free survival, and aGVHD grade II–IV (Clausen et al., 2010).

Further studies assessed the effect of the presence of KIR2DS5 gene in addition to heterozygosity in HLA-C1 or C2 compared to homozygosity. Van der Meer A. et al. conducted a study on a homogeneous group of CML patients (in first chronic phase) who received HLA identical sibling SCT (Van der Meer et al., 2008). The data showed clear differences in transplant outcome between patients having both ligands (C1 and C2) as compared to patients having only one ligand (C1 or C2). In the latter group, the stimulatory KIR2DS5 gene was associated with improved leukemia-free survival and lower relapse rates. These data indicate a role for an NK mediated anti-CML response after HLA identical sibling SCT that is influenced by KIR ligands and more importantly, by stimulatory KIRs present in the donor (Van der Meer et al., 2008).

The role of KIR2DS5 was evaluated as well by Wang H. et al. who assessed the impact of donor KIR and recipient HLA genotypes on outcome following haploidentical HSCT (non T-cell-depleted in vitro transplant from haploidentical donor) in patients with hematologic diseases (Wang et al., 2008). Donor/recipient KIR/HLA subgroup was assessed by donors KIR and recipients HLA-Bw4, Cw1 group, and Cw2 group alleles. The results showed that hematopoietic reconstitution, incidence of GVHD, DFS, infection, and TRM were not significantly different between every two groups. The donor activating KIR2DS5 positive group had higher two-year DFS compared with the negative group. It was concluded that KIR/HLA genotypes between donor and recipient influence the outcome following haploidentical HSCT. Donor activating KIR2DS5 may improve DFS in non TCD haploidentical HSCT (Wang et al., 2008).

The presence of another gene, KIR2DS2, in the donor in addition to HLA-C1C2 in the recipient was assessed by Ludajic K. et al. in patients with various hematological malignancies including myeloid (AML, CML, MDS), lymphoid (ALL, NHL, HL, CLL), and multiple myeloma, transplanted with 12/12 HLA matched grafts from unrelated donors (Ludajic et al., 2009). Transplantation of either or both HLA-C1 and C2 patients with KIR2DS2 positive grafts were found to be associated with a decreased risk of aGVHD (II–IV). Thus, this study provided evidence for the modification of aGVHD risk by KIRs and their ligands (Ludajic et al., 2009).

## 1.3. KIR in HSCT: negative outcomes

On the other hand, certain KIR receptors and associated ligands were predictive of a negative outcome. Again, we review the negative outcomes according to the different models.

### 1.3.1. Ligand-ligand model

In the same study aforementioned by Kröger N. et al., on patients with leukemia who received standard myeloablative conditioning followed by in vivo TCD (ATG) unrelated SCT, KIR ligand mismatch was found to have a significantly higher treatment related mortality leading to decreased OS and DFS (Kröger et al., 2006). Moreover, Zhao

XY. et al. evaluated the prognostic implication of the KIR ligand mismatch in leukemia patients undergoing unmanipulated HLA-mismatched/haploidentical blood and marrow HSCT. They found that KIR ligand mismatch was an independent risk factor for the aGVHD (Zhao et al., 2008). In addition, compared to those without KIR ligand mismatch, patients with KIR ligand mismatch had the more adverse effect of 'high' dose T cells ( $> 1.48 \times 10^5$ /kg) on aGVHD, and had more incidence of aGVHD with HLA-C mismatch. Since multivariate analysis demonstrated that high risk leukemia was the only predictor for TRM, relapse, and OS, the effect of KIR ligand mismatch on prognosis in standard and high risk patients was further analysed. The differences in TRM and OS between patients with and without KIR ligand mismatch were most striking for standard risk patients. They concluded that KIR ligand mismatch is a poor prognosis factor for patients who underwent HLA mismatched HSCT, and is a useful parameter for donor selection (Zhao et al., 2008).

The impact of KIR-ligand mismatch on acute GVHD was further investigated in a study by De Santis et al. whereby KIR ligand mismatching in the rejection direction was strongly associated with an increased probability of rejection subsequent to engraftment (De Santis et al., 2005). The prevalence of aGVHD (grades III–IV) was found to be significantly higher and to occur significantly earlier when there was ligand mismatching (for iKIR) in the GVH direction. However, higher TRM and lower DFS rates were associated with ligand mismatching regardless of the mismatch direction (De Santis et al., 2005).

KIR-ligand mismatch of particular aKIRs was the focus of interest in a study by Giebel S. et al. where they evaluated the impact of donor and recipient aKIR genes on outcome of allogeneic HSCT for patients with hematological malignancies (AML, ALL, CML, MDS, HL) (Giebel et al., 2009). They found that mismatches of particular aKIRs such that the patient was negative and the donor was positive (P-D+) resulted in increased risk of acute (KIR2DS1) and chronic (KIR2DS3) GVHD as well as relapse (KIR2DS5). KIR2DS1 incompatibility in the same direction in the presence of HLA-C-group 2 ligand in recipient was associated with reduced OS and DFS. Among six evaluated patients, expression of activating KIRs on NK cells and T cells was particularly prominent for those developing intestinal GVHD. These findings indicate that the presence of particular activating KIRs in donor with their absence in recipient enhances GVHD, which is not accompanied by graft-versus-leukemia effect (Giebel et al., 2009). Thus, evaluation of activating KIR genotype may allow optimization of both donor selection and transplantation procedure in order to avoid GVHD.

In addition, some studies assessed the effect of KIR2DL ligand mismatch on outcome, namely the incidence of GVHD and leukemia relapse. For example, Morishima et al. found that KIR2DL ligand mismatch in the GVHD direction (KIR-L-MM-G) increased in ALL (Morishima et al., 2007). An increased rejection rate was observed in KIR2DL ligand mismatch in the host-versus-graft direction. Acute GVHD was increased not only in the mismatch of HLA-A, -B, -C, and -DPB1, but also in KIR-L-MM-G. In addition, this mismatch resulted in increased mortality. Morishima et al. concluded that not only the mismatch of HLA-C and -DPB1, but also KIR-L-MM-G affected leukemia relapse, which should be considered based on leukemia cell type. Furthermore, KIR-L-MM induced adverse effects on aGVHD and rejection, and brought no survival benefits to patients with T-cell-replete UR-BMT (Morishima et al., 2007).

In one of a few studies, molecular relapse was the outcome of interest. To examine how KIR-ligand mismatch effects molecular response (MR), Elmaagacli AH. et al. compared the occurrence of bcr-abl-positive reverse transcriptase polymerase chain reaction (RT-PCR) results in 236 patients with CML after HLA-identical (n = 158) (group 1), HLA class I antigen mismatched and KIR-ligand matched (n = 49) (group 2), and HLA class I antigen mismatched and KIR-ligand mismatched (n = 29) (group 3) HSCT (Elmaagacli et al., 2005). This was a retrospective single centre study whereby MR was evaluated using the RT-PCR method for the detection of bcr-abl transcripts. In the first group, 84% of the patients

were in the first chronic phase of CML while 67% and 39% of patients in groups 2 and 3, respectively, were in this phase. A hematologic relapse occurred in 13% of patients in group 1, 4% in group 2, and 0% in group 3. KIR mismatches were confirmed to be a strong independent predictor for the incidence of MR after transplantation although the five-year survival, did not vary greatly between the three groups (67% in group 1, 52% in group 2, and 66% in group 3) (Elmaagacli et al., 2005). These results still suggest that KIR-ligand mismatch is an important prognostic factor in the occurrence of molecular relapse after transplantation for CML.

### 1.3.2. Haplotype model

Negative outcomes were found in donors with the KIR haplotype A. Elaborating on that point, Bao X.J. et al. found that in the haplotype A/A group, a higher risk of aGVHD, especially grade III–IV, was observed when the donor was homozygous for the full-length expressed KIR2DS4\*00101 allele. A high expression of inhibitory KIR (2DL1 and 3DL1) in the early stages (<90 days) after transplantation correlated with the development of aGVHD (Bao et al., 2010a, 2010b). These findings indicated a significant association of full-length KIR2DS4 or KIR2DL1/3DL1 expression with the occurrence of aGVHD (Bao et al., 2010a, 2010b). In addition, dynamic detection of KIR2DL1/3DL1 expression would therefore be beneficial for prediction of aGVHD after transplantation.

The activating donor receptor KIR2DS4 is a more prevalent KIR in haplotype A than B. The KIR2DS4 variants differ in exon 5 and play a role in HSCT. Bao X. et al. conducted a study on patients who received T-cell-depleted HSCT and their unrelated donors (Bao et al., 2010a, 2010b). The majority (92.7%) were positive for KIR2DS4. Four of the nine known KIR2DS4 alleles, KIR2DS4\*00101, \*003, \*004, and \*007, were identified. In the haplotype A/A group, a higher risk of aGVHD was seen when the donor carried two full-length KIR2DS4 alleles. These findings suggested that the expression of full-length 2DS4 (\*001) in A/A group may contribute to a worse clinical outcome after UR-HSCT. These data would be beneficial for the selection of suitable donors (Bao et al., 2010a, 2010b).

KIR haplotype B was also reported to be associated with negative outcomes. As a matter of fact, Cooley S. et al., found that B/x donors HSCT were associated with a higher incidence of chronic GVHD (but not of acute GVHD, relapse, or TRM) (Cooley et al., 2009). Within KIR haplotype B, the effect of the different donor activating KIRs, namely KIR2DS1, KIR2DS2, KIR2DS3, and KIR2DS5, was tackled in many studies. Regarding the donor activating receptors KIR2DS1 and KIR2DS2, Duan LN et al. found that the acute and severe GVHD was related to the existence of activating receptors of KIR2DS1/2DS2 (Duan et al., 2007). The incompatibility group was accompanied with frequent acute and severe GVHD and less relapse and vice versa for the compatibility group. One patient died after BMT among the 14 mismatched KIR ligand group suffering from myelogenous leukemia while 4 patients out of 12 patients died in the matched group (Duan et al., 2007). The association of donor KIR2DS2 with negative outcome was reiterated in another study, however, in the specific setting of HLA-C2 homozygous recipients. A study by Cook et al. was performed on patients with myeloid and lymphoid diseases who received HLA-matched sibling HSCTs. In the cases of myeloid disease (AML, CML, and MDS), OS was worse in patients homozygous for HLA-C2 than in patients who carried a HLA-C1 allele. Moreover, this effect is seen only when the donor additionally carries the activating KIR gene KIR2DS2 (Cook et al., 2004). Therefore, in HLA-matched sibling HSCT for myeloid leukemia, patients homozygous for C2 alleles receiving a graft from a donor carrying the KIR2DS2 gene have a significantly decreased chance of survival (Cook et al., 2004).

Concerning the donor activating receptor KIR2DS3, and according to a study by Zhao X. et al., patients receiving activating KIR2DS3-positive donors had a significantly higher incidence of acute and chronic GVHD and the presence of donor-activating KIR2DS5 was associated with

increased aGVHD (Zhao et al., 2007). A similar finding by Wu GQ et al. was that the presence of donor activating KIR2DS3 gene was associated with increased relapse risk, decreased OS and DFS in myeloid disease, thus concluding that the presence of KIR2DS3 in the donor was an important risk factor for myeloid leukemia (Wu et al., 2010). As for the donor activating receptor KIR2DS5, Van der Meer A. et al. found that in CML patients carrying both ligands, KIR2DS5 was associated with reduced LFS and higher relapse rate (Van der Meer et al., 2008).

The same findings of negative impact of receptors KIR2DS2 through KIR2DS5 were confirmed by Kim HJ et al. who found that the KIR2DS2 gene and the 2DS4\*003 allele were closely correlated with acute GVHD and that the KIR2DS3–2DS5 dual genes were more often involved in a variety of transplant-related complications (Kim et al., 2007a, 2007b). Therefore, the presence of the inhibitory KIRs 2DL1 and 3DL1, as well as the presence of the activating KIR 2DS4, in haplotype A, and the presence of the inhibitory KIRs 2DS1, 2DS2, 2DS3, and 2DS5 in haplotype B are associated with negative outcomes regarding bone marrow stem cell transplant.

### 1.3.3. Missing-ligand model

According to Miller et al., missing 1 or more KIR ligands had no independent effect on aGVHD except in patients with CML > 1 year from diagnosis where it was associated with an unexpected high incidence of grade 3–4 aGVHD (from 30% to a rate of 44%) (Miller et al., 2007). They speculated that, in this cohort, perhaps T cells in the graft were active immediately after transplantation, establishing aGVHD before NK cells had the opportunity to kill host Antigen presenting cells. The higher rate of aGVHD in the CML cohort may be explained by the expanded myeloid pool with more host APCs capable of presenting alloantigen to donor T cells (Miller et al., 2007).

On the other hand, Ludajic K. et al. found that a missing HLA-C2 ligand for donor inhibitory KIR2DL1 was significantly associated with an increased risk of aGVHD (II–IV), as were the A/A KIR haplotypes in patients and donors in HLA-C1CX and in HLA-Bw4(–) patients (Ludajic et al., 2009). Clausen J. et al. were interested in studying the different impacts on peripheral blood stem cell transplant (PBSCT) as compared to bone marrow stem cell transplant (BMSCT) (Clausen et al., 2012). They analysed PBSCT and found a poor progression-free survival in homozygous HLA-C group 2 (C2/2) recipients (compared to BMT). These data suggest opposite effects of missing KIR ligands in BMT vs. PBSCT (Clausen et al., 2012). However, larger studies are still required to reassess whether BMT should be preferred to PBSCT as an option for C2/C2 recipients.

## 1.4. KIR in HSCT: neutral outcomes

We divide again the neutral outcomes according to the different KIR models.

### 1.4.1. Ligand-ligand model

First, no effect was seen pertaining to the *ligand-ligand model*. Although KIR-ligand mismatch has been clearly associated with better survival in haploidentical allogeneic SCT for AML, its role in unrelated HLA-mismatched allogeneic SCT is more controversial. Schaffer M. et al. were interested in the latter role, as they underwent a retrospective analysis of KIR-ligand matched (n = 167) and mismatched (n = 23) unrelated allogeneic SCTs for hematologic malignancies performed at a single centre (Schaffer et al., 2004). They observed that KIR-ligand mismatch was associated with increased TRM, thus leading to decreased overall survival. The higher TRM was due to a higher rate of infections, while the incidence of GVHD and leukemic relapse was not significantly different between the two groups. They concluded that the presence of donor-derived, alloreactive NK cells may interfere with immunity to infection in the early post-transplantation period (Schaffer et al., 2004). As we can see from this study, both neutral and

negative outcomes can occur in unrelated allogeneic SCT for hematologic malignancies.

In other instances, KIR-ligand mismatch was consistently found to have neutral outcomes in unrelated donor transplantations. This can be illustrated in a study by Farag et al. conducted on unrelated donor transplantations for myeloid malignancies (AML, CML, MDS) where donor–recipient pairs were HLA-A, -B, -C, and -DRB1 matched; GVH KIR ligand–mismatched; host-versus-graft (HVG) KIR ligand–mismatched; and HLA-B and/or –C–mismatched but KIR ligand–matched (Farag et al., 2006). Treatment-related mortality (TRM), treatment failure, and overall mortality were lowest after matched transplantations. Patients who received grafts from donors mismatched at the KIR ligand in the GVH or HVG direction and mismatched at HLA-B and/or C but matched at the KIR ligand had similar rates of TRM, treatment failure, and overall mortality. There were no differences in leukemia recurrence between the four groups (Farag et al., 2006). Therefore, these results do not support the choice of an unrelated donor on the basis of KIR ligand mismatch determined from HLA typing.

Furthermore, Weisdorf D. et al. studied patients with advanced/high-risk myeloid malignancies (AML, CML, or MDS) lacking either related or well-matched unrelated donors (UR). The patients were mismatched at 1–3 of 10 HLA loci with their donors; all were mismatched at HLA-C (Weisdorf et al., 2012). The cumulative incidence of grade IV aGVHD, chronic GVHD, and relapse were unaffected by KIR ligand mismatch versus KIR ligand match. Two-year survival and leukemia-free survival were each 40% and was similar in KIR ligand matched or mismatched patients. T cell recovery and NK cell proliferation and functional maturation were not altered by KIR ligand match or mismatch status (Weisdorf et al., 2012). Improvements in peritransplantation disease control and additional measures to augment the allogeneic graft-versus-leukemia effect are still required.

Moreover, Sivula J. et al. investigated the effect of KIR ligand incompatibility retrospectively in 186 UR-SCT performed in Finland during years 1993–2004 (Sivula et al., 2007). No clear evidence for a better outcome in cases with KIR ligand incompatibility was obtained. TRM was 64% in the GVHD direction KIR ligand–mismatched group and 33% in the KIR ligand–matched group, however, this difference was not statistically significant. Consequently, no support could be obtained for a beneficial effect of KIR ligand incompatibility in this set of unrelated donor transplantations (Sivula et al., 2007). Neutral outcomes were also found by Wu GQ et al. whereby KIRs and their ligands had no effect in patients with lymphoid disease after unrelated HSCT (Wu et al., 2010). Wongwuttisaroj N. et al. also found that there was no effect of KIR gene mismatch and missing ligand on the outcome regarding GVHD, relapse, and OS (Wongwuttisaroj et al., 2012).

Farag SS. et al. investigated the effect of KIR ligand mismatching on the outcome of unrelated donor transplantation. They compared the outcomes after 1571 unrelated donor transplantations for myeloid malignancies where donor–recipient pairs were HLA-A, -B, -C, and -DRB1 matched (n = 1004), GVH KIR ligand–mismatched (n = 137), host-versus-graft (HVG) KIR ligand–mismatched (n = 170), and HLA-B and/or –C–mismatched but KIR ligand–matched (n = 260) (Farag et al., 2006). Treatment-related mortality (TRM), treatment failure, and overall mortality were lowest after matched transplantations. However, patients who received grafts from donors mismatched at the KIR ligand in the GVH or HVG direction and mismatched at HLA-B and/or C but matched at the KIR ligand had similar rates of TRM, treatment failure, and overall mortality. There were no differences in leukemia recurrence between the four groups (Farag et al., 2006). Therefore, these findings do not support the choice of an unrelated donor based on KIR-ligand mismatch determined from HLA typing.

### 1.4.2. Haplotype model

Neutral outcomes were also found in what pertains to the *haplotype model*. In fact, a study by Björklund et al. revealed that the presence of iKIRs for non-self HLA class I ligands in patients with myeloid

malignancies (AML and MDS), who received T cell-replete SCT from HLA-matched sibling donors, was found to have no effect on DFS, incidence of relapse, or GVHD (Björklund et al., 2010).

#### 1.4.3. Missing-ligand model

Finally, regarding the *missing-ligand model*, both neutral and positive outcomes were found in one study by Hsu, K.C. et al. on patients with HLA identical related donor transplant as the outcomes differed according to the type of hematologic malignancy. This study consisted of 178 patients receiving T-cell-depleted HLA-identical sibling transplants for AML, CML, ALL or MDS and the results of comparison of donor KIR genotype with HLA genotype demonstrated that 62.9% of the patients lacked an HLA ligand for donor iKIR (Hsu et al., 2005). Lack of HLA ligand for donor iKIR (*missing KIR ligand*) had no effect on DFS, OS, or relapse in patients receiving transplants for CML and ALL. In patients with AML and MDS, however, there was a significant missing KIR ligand effect on DFS and OS. Incidence of relapse was also lower in patients with AML and MDS who lacked the HLA ligand for donor iKIR. AML and MDS patients lacking 2 HLA ligands for donor iKIR had the highest DFS and OS. There was no significant contribution of donor aKIR to transplantation outcome in these patients (Hsu et al., 2005). These data indicate that the absence of Class I ligand in the recipient for donor iKIR can be a prognostic factor for transplantation outcome in HLA-identical sibling transplantation and that the lack of HLA-C or -B ligands for donor iKIR can contribute to better outcomes for patients with AML and MDS.

Clausen J. et al. hypothesized that the impact of missing KIR ligands on RFS and OS in T cell replete peripheral blood SCT (PBSCT) differs from that in the T cell depleted BMT setting (Clausen et al., 2010). They evaluated HLA-identical sibling transplantations for hematologic malignancies. Their findings demonstrate that OS and RFS for the heterozygous HLA-C group KIR ligand status were not inferior compared with patients missing either C1 or C2. Similarly, OS and RFS of Bw4-positive patients was not lower than that of patients missing a Bw4 ligand to KIR3DL1. They concluded that the mechanism favouring the missing KIR ligand constellation in T cell depleted BMT may not operate in T cell replete PBSCT. Nevertheless, the reasons for this differential effect remained unresolved (Clausen et al., 2010).

## 2. Conclusion

This review article is the first in the literature that reports on the association of KIR genotype with outcome of peripheral blood and bone marrow HSCT outcomes for hematologic malignancies using a four dimensional level of analysis based on: the *ligand-ligand model*, the *missing-ligand model*, the *receptor-ligand model*, and the *haplotype model*. As more progress is registered in research pertaining to bone and peripheral blood stem cell transplantation especially with the increasing reports of success rates in haploidentical transplantations for various clinical disorders, KIR genotype profiling may soon find its place as a must-do diagnostic test in histocompatibility laboratory services as soon as the data of more publications is revisited again probably through another review research article.

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## Abbreviations

- ATG: antithymocyte globulin  
 AML: acute myelogenous leukemia  
 ALL: acute lymphoblastic leukemia  
 APC: Antigen presenting cells  
 BMT: bone marrow transplant  
 CML: chronic myelogenous leukemia  
 DFS: disease-free survival  
 EFS: event-free survival  
 GVHD: graft-versus-host disease  
 aGVHD: acute graft-versus-host disease  
 cGVHD: chronic graft-versus-host disease  
 GVT: graft-versus-tumor  
 HL: Hodgkin's lymphoma  
 HLA: Human Leukocyte Antigen  
 HSCT: Hematopoietic Stem Cell Transplantation  
 HVG: host-versus-graft  
 KIR: Killer-cell Immunoglobulin-like Receptor  
 aKIR: activating Killer-cell Immunoglobulin-like Receptor  
 iKIR: inhibitory Killer-cell Immunoglobulin-like Receptor  
 LFS: leukemia-free survival  
 LRC: Leukocyte Receptor Complex  
 MDS: myelodysplastic syndrome  
 MHC: Major Histocompatibility Class  
 MM: multiple myeloma  
 MR: molecular relapse  
 NHL: non-Hodgkin's lymphoma  
 NK cells: Natural Killer Cells  
 OS: overall survival  
 PBSC: peripheral blood stem cell transplants  
 PFS: progression-free survival  
 RFS: relapse-free survival  
 TCD: T-cell depleted  
 TRM: transplant-related mortality  
 UR: unrelated donor  
 UR-BMT: unrelated donor bone marrow transplant